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| 10/530,512 | 04/06/2005 | Charles Keller | 007180-65 | 6728 |

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| EXAMINER | |
|---|---|
| WILDER, CYNTHIA B | |

| ART UNIT | PAPER NUMBER |
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| 1637 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/530,512 | KELLER ET AL. | |
| | Examiner | Art Unit | |
| | CYNTHIA B. WILDER | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,18,25,26 and 31-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,18,25,26,31 and 33* is/are rejected.

7)☒ Claim(s) *32,34 and 35* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

1. Applicant's amendment filed 8/5/2008 is acknowledged and has been entered. Claims 1, 18, 25, 26 and 31 have been amendment. Claims 2-17, 19-24, 27-30 and 36-70 have been canceled. Claims 1, 18, 25-26, 31-35 are pending. . All of the arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. This action is made non-final as the new grounds of rejections presented in this Office action were not necessitated by Applicant's amendment of the claims. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

***Previous Objections and Rejections***

3. The claim rejection under 35 USC 112 first paragraph as lacking enablement is withdrawn in view of Applicant's amendment. The claim rejection under 35 USC 112 second paragraph is withdrawn in view of Applicant's amendment. The prior art rejections under 35 USC 102(b) as being anticipated by Jourenkova-Mironova et al is maintained and discussed below. The prior art rejection under 35 USC 102(b) as being anticipated by Ko et al is withdrawn in view of Applicant's amendment and cancellation of the claims. The prior art rejection under 35 USC 102(a) as being anticipated by Lan et al is maintained for the claim 1, but withdrawn for the claim 14 in light of Applicant's cancellation of the claims. The prior art rejection under 35 USC 102(a) as being anticipated by Buch et al is withdrawn in view of Applicant's amendment and

cancellation of the claims. The prior art rejections under 35 USC 103(a) are all withdrawn in view of Applicant's cancellation of the claims.

***Claim Rejections - 35 USC § 102(b)***

4. Once again, claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Jourenkova-Mironova et al (Int. J. Cancer, vol. 81, pages 44-48, 1999). Regarding claim 1, Jourenkova-Mironova et al teach a method for detecting GST alleles present in a patient comprising the steps of: obtaining a biological sample from the patient; isolating genomic DNA from the sample; performing PCR amplification of a portion of the DNA to detect GSTM1 alleles; performing PCR amplification of a portion of the DNA to detect GSTM3 and GSTT1 alleles; performing PCR amplification of a portion of the DNA to detect GSTP1 polymorphisms; and detecting GSTM1, GSTM3, GSTT1 and GSTP1 polymorphic alleles in the DNA obtained from the PCR amplification step (abstract and section entitled "Materials and Methods", beginning at col. 2 of page 44 to col. 1 on page 46). Therefore, Jourenkova-Mironova et al meet the limitations of claim 1.

***Claim Rejections - 35 USC § 102(a)***

5. Once again, caim 1 is rejected under 35 U.S.C. 102(a) as being anticipated by Lan et al (Pharmacogenetics, vol. 22, pages 655-661, November 11, 2001). Regarding claim 1, Lan et al teach a method for detecting GST alleles present in a patient comprising the steps of: obtaining a biological sample from the patient; isolating genomic DNA from the sample; performing PCR amplification of a portion of the DNA to detect GSTM1 alleles; performing PCR amplification of a portion of the DNA to detect GSTM3 and GSTT1 alleles; performing PCR amplification of a portion of the DNA to detect GSTP1 polymorphisms; and detecting GSTM1, GSTM3, GSTT1 and GSTP1 polymorphic alleles in the DNA obtained from the PCR amplification step (see section entitled "Materials and Method", page 656-657).

Therefore, Lan et al meets the limitations of the claims recited above.

***Response to Arguments***

6. Applicant traverses the rejection on the following grounds: Applicant states that the amendment overcomes the prior art rejections because the amendments to contain specific alleles are not all disclosed in the prior art rejections made of record. Applicant states that accordingly the rejections appear to be moot.

7. All of the arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons that follow. In regards to Applicant's arguments that the claims recite specific alleles, it is noted applicant does not provide a limiting definition or structure which corresponds to the alleles recited in the instant claims. The specification teaches that these alleles represent non-null and null alleles or absent

alleles. More specifically, the claims do not provide a recitation of any specific amino acid or nucleotide change that is indicative of the polymorphic alleles represented as GSTM1*A or GSTT1*0. The courts have established that during patent examination the pending claims must be interpreted as broadly as their terms reasonably allow (*In re Zletz, 893 F.2d 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989).* In this case, given the broadest reasonable interpretation of the claims as written, the limitations are simply interpreted as non-null and null or absent alleles.

With regards to Jourenkova-Mironova et al, the reference teaches a genotyping assay comprising performing PCR amplification to detects polymorphic alleles of GSTM1, GSTM3, GSTT1 and GSTP1, wherein said alleles are non-null and null alleles of the GSTM1, GSTM3, GSTT1 and GSTP1 (see section entitled "Results" at pages 45-46, especially the Table II at page 46 {GSTM1*1 or GSTM1*0 would be represented as GSTM1 (null OR for null[6]); GSTM3*A or GSTM*B would be represented as GSTM3 AA or GSTM3 BB (non-null alleles); GSTP1*A or GSTP1*B or GSTP1*C or GSTP1*D would be represented as GSTP1 AA, BB, GG or AG; GSTT1*0 or GSTT1*1 would be represented as the null alleles}).

With regards to Lan, the same arguments applied above, applies in this case. Lan teaches the polymorphic alleles as encompassed by the claims in the "Discussion presented at pages 658-660 and especially in the TABLE 2).

Thus applicant's arguments are not found persuasive and accordingly, the rejections are maintained.

***New Ground(s) of Rejections***

***Claim Rejections - 35 USC § 103***

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jourenkova-Mironova et al as previously applied above in view of Nishimura et al (JP 2002058483, 18 September 2002) in view of Ali-Osman et al (5968737, October 1999) and further in view of Buck et al (Biotechniques, col. 27, pages 528-536, September 1999) . Regarding claim 18, Jourenkova-Mironova et al teach a method for detecting GST alleles present in a patient comprising the steps of: obtaining a biological sample from the patient; isolating genomic DNA from the sample; performing PCR amplification of a portion of the DNA to detect GSTM1 alleles; performing PCR

amplification of a portion of the DNA to detect GSTM3 and GSTT1 alleles; performing PCR amplification of a portion of the DNA to detect GSTP1 polymorphisms; and detecting GSTM1, GSTM3, GSTT1 and GSTP1 polymorphic alleles in the DNA obtained from the PCR amplification step (abstract and section entitled "Materials and Methods", beginning at col. 2 of page 44 to col. 1 on page 46).

Jourenkova-Mironova does not expressly teach wherein the method comprises using a primer selected from the group consisting of the sequences recited in SEQ ID NOS: 13-23.

Nishimura et al teach primer and probes for use in the measurement of glutathione-S-transferase which participates in the glutathione conjugation in Homo sapiens. Nishimura teach a sequence substantially identical to the sequence of SEQ ID NO: 13 and SEQ ID NO: 14 (see sequence alignment below and the primer sequence for the human GSTP1 gene, Sequence 1):

```
SEQ IN NO: 13          7 GACCTCCGCTGCAAATACA 25
                           ||||||||||||||||||
Nishimura et al        3 GACCTCCGCTGCAAATACA 21


SEQ ID NO: 14          1 GACCTCCGCTGCAAATACA 19
                           ||||||||||||||||||
Nishimura et al        3 GACCTCCGCTGCAAATACA 21
```

Ali-Osman et al teach cDNA and genomic clones for three variants of GST-π and new compositions, such as GST-π genes, oligonucleotides, peptides and antibodies for the detection and treatment of certain classes of tumors using amplification and hybridization techniques (see a. Ali-Osman et al teach a sequence substantially

identical to the sequence of SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19 (see alignment below and SEQ ID NOS: 5, 29, 1, respectively):

```
SEQ ID NO: 16            1 GACCTCCGCTGCAAATACG 19
                           ||||||||||||||||||
Ali-Osman et al        307 GACCTCCGCTGCAAATACG 325


SEQ ID NO: 17            6 TCAGCCCAAGCCACCTGA 23
                           ||||||||||||||||||
Ali-Osman et al          3 TCAGCCCAAGCCACCTGA 20


SEQ ID NO: 18            1 TCAGCCCAAGCCACCTGA 18
                           ||||||||||||||||||
Ali-Osman et al          3 TCAGCCCAAGCCACCTGA 20


SEQ ID NO: 19           10 TGGTGTCTGGCAGGAGGT 27
                           ||||||||||||||||||
Ali-Osman et al     2410 TGGTGTCTGGCAGGAGGT 2427
```

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed oligonucleotide sequences simply represent structural homologs of the oligonucleotides taught by the prior art recited above and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with

improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes "Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents, Buck et al expressly provides a general teaching of evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18-mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the

primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95-control primers functioned, which represent 1/3 of all possible primers in the target region.

This clearly shows that every oligonucleotide sequence would have a reasonable expectation of success since they represent sequences that are from eleven to twenty nucleotides in length corresponding to the nucleotides of the instant invention.

11. Claims 25, 26, 31 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jourenkova-Mironova et al as previously applied above in view of Sprenger (citation made of record in prior Office action). With regards to claims 25, 26, 31, Jourenkova-Mironova et al teach a method for detecting GST alleles present in a patient comprising the steps as previously described above wherein GSTM1, GSTM3, GSTT1 and GSTP1 polymorphic alleles are detected.

Jourenkova-Mironova et al do not expressly teach wherein long range PCR is used to distinguish between different alleles.

Sprenger et al teach a method of using long range PCR to distinguish between different GSTT1 alleles. Sprenger et al teach wherein the concept can be applied to other GST alleles, such as GSTM1. Sprenger et al teach that long range PCR allows one to home in on the exact position of the mutation using various sets of PCR primers close to the mutation site (see e.g., 0050, 0054, and 0063).

One of ordinary skill in the art at the time of the claimed invention would have been motivated to have utilized long range PCR in the method of Jourenkova-Mironova et al to distinguish between specific alleles based on the teachings of Sprenger et al that long range PCR allows one to specifically detect the exact location of the mutation. One of ordinary skill in the art at the time of the claimed invention would have been motivated to use long range PCR to increase specificity of distinguishing between mutated alleles of a specific gene associated with a specific disease or condition.

Regarding claim 33, Sprenger et al teach repeating the assay if the amplification fails (0051 and 054).

***Conclusion***

12. Claims 1, 18, 25, 26, 31 and 33 have been rejected. Claims 32, 34 and 35 are objected because they depend from rejected claims. Any inquiry concerning this communication or earlier communications from the examiner should be directed to CYNTHIA B. WILDER whose telephone number is (571)272-0791. The examiner can normally be reached on a flexible schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cynthia B. Wilder/

Examiner, Art Unit 1637